IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
PATENT APPLICATION EXAMINING OPERATIONS

Appl. No.	: 09/770,562	Confirmation No. 8513
Applicant	: Curatolo et al.	
Filed	: January 26, 2001	
Title	: SOLID PHARMACEUTICAL DISPERSIONS WITH ENHANCED BIOAVAILABILITY	
TC/A.U.	: 1618	
Examiner	: Fubara, Blessing M.	
Docket No.	: 0003.0562/PC9674A	
Customer No.	: 00152	

APPEAL BRIEF

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November 19, 2009

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Commissioner for Patents
P.O. Box 1450
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Real Party in Interest

The real party in interest by virtue of assignment is Bend Research, Inc., an Oregon corporation.

Related Appeals or Interferences

There are no related appeals or interferences.

Status of Claims

Claims 2-3, 5-22, 24-27 and 39-48 have been cancelled and claims 28-35 and 38 have been withdrawn. Claims 1, 4, 23, 36-37, 49-51 and 53-56 are pending and their rejection is appealed; a copy of the claims on appeal is set forth in the Claims Appendix.

Status of Amendments

All amendments have been entered.

Summary of Claimed Subject Matter

Claim 1, the only independent claim in the application, is directed to a composition of matter comprising a spray-dried dispersion, the dispersion consisting of a low-solubility drug and the polymer hydroxypropyl methylcellulose acetate succinate (HPMCAS). Published US Application 2002.009494A1 ('494), paragraphs [0012], [0085] and [0086]. The drug is molecularly dispersed and amorphous in the dispersion. '494 paragraph [0027]. The dispersion has a drug:polymer ratio between 1:04 and 1:20. '494 paragraph [0049].

Grounds of Rejection to be Reviewed on Appeal

There are five issues on appeal:

1. whether claims 1, 4, 49-51 and 53-56 are anticipated under §102(b) by **Miyajima** EP 0 344 603;

2. whether claims 1, 4, 49-51 and 53-56 are anticipated under §102(a) by **Kigoshi** EP 0 784 974;

3. whether claims 1, 4, 49-51 and 53-56 are anticipated under §102(b) by **JP 57-176907**.

4. whether claims 1, 23 and 50-51 are rendered obvious under §103(a) by **Miyajima** or **Kigoshi**; and

5. whether claims 1, 4, 36-37, 49-51 and 53-56 are rendered obvious under §103(a) by the combination of **Kigoshi,** the **PubMed** Abstract of an article by Madhussodanan *et al.* and **Bymaster** US 6,147,072.

ARGUMENT

Prior Art Relied Upon

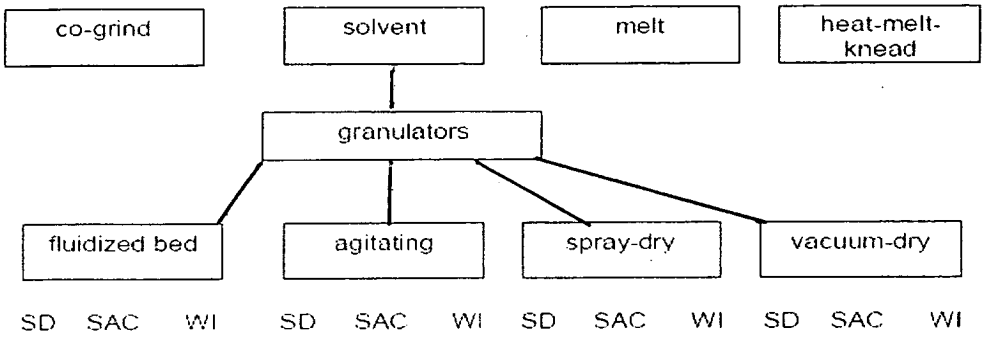
From applicants' standpoint, the most compelling shortcomings of the five prior art references relied upon are as follows. Further shortcomings are discussed *infra*.

Miyajima discloses a pharmaceutical composition comprising a solvate of the drug NZ-105 and HPMCAS. The patent is silent as to the state of the drug in the composition. Although it is broadly stated at the bottom of page 4 that the composition may be prepared by dissolving the drug and HPMCAS in an organic solvent, then removing the solvent by vacuum-drying, freeze-drying or spray-drying, the reference does not in fact teach how to make an NZ-105 composition by spray-drying. The only

enabling disclosure with specific details on how to formulate the NZ-105 compositions is found in the six Examples. Five of the six Examples (Examples 1-5) dissolve three components (drug, HPMCAS and urea) in a mixed organic solvent, then spray this solution onto a fourth component, i.e., a granular support (calcium hydrogen phosphate anhydride or crystalline lactose) using a fluidized bed granulation apparatus. Thus, Examples 1-5 show how to make a four-component composition prepared by a method other than spray-drying. In the case of Example 6, the drug and HPMCAS are dissolved in an organic solvent and lactose is dispersed into the solution, which liquid mixture is then dried *in vacuo*. Thus Example 6 shows how to make a three-component composition also prepared by a method other than spray-drying.

Kigoshi discloses a solid amorphous dispersion of a poorly water-soluble xanthine derivative and polymer. In the paragraph bridging pages 3 and 4, seven classes of polymers are listed as suitable for forming the dispersions. One of the seven classes is cellulosics, and 10 different cellulosic compounds and derivates are named, including HPMCAS. In all, 22 specific polymers are listed. The dispersions can be prepared by any of four methods: co-grinding, solvent, melting or heat-melt-kneading. Page 4, lines 16-17. The "solvent method" uses any of four types of granulators: fluidized bed, agitating, spray-dry or vacuum-dry. Page 4, lines 37-38. To use one of the solvent methods, a spray solution is prepared by dissolving the drug and polymer in an organic solvent, then adding a surfactant. Page 4, lines 39-40. The spray solution is then either spray-dried, sprayed onto an absorbent carrier or injected into water. Page 4, lines 49-50. A recap of the universe of possible processes suggested by Kigoshi for the preparation of the dispersions is set out below in graphic form.

KIGOSHI METHODS



SD = spray-dry
SAC = sprayed onto absorbent carrier
WI = water injection

Thus, a total of 15 different processes of making dispersions are named by Kigoshi.

Notwithstanding the foregoing broad statements on how to form the dispersions, comprising at least 22 polymer choices and 15 process choices, the reference does not in fact teach one skilled in the art how to prepare (*i*) any two-component dispersion of drug and HPMCAS or (*ii*) any dispersion by spray-drying. Specifically, three of the five Examples of dispersion preparation (Examples 1-3) show how to make three-component dispersions of drug, methacrylate copolymer and lactose prepared by fluid bed granulation, and the other two (Examples 4 and 5) show how to make dispersions of drug and methacrylate copolymer by heat-melt-kneading using an extruder.

JP 57 discloses compositions of the low solubility drug AS-56C and HPMCAS wherein the drug is stated to be amorphous in the composition. Although such

compositions are stated to be prepared by spray drying, no specifics are disclosed as to how the spray drying was accomplished.

The **PubMed** Abstract merely teaches that risperidone is a safe antipsychotic medication for the elderly. Nothing is stated as to its solubility or dosage form.

Bymaster merely teaches that risperidone and ziprasidone are two of six atypical antipsychotics that may be combined with one or more serotinin reuptake inhibitors for treatment of psychoses.

Anticipation of Claims 1, 4, 49-51 and 53-56 by Miyajima or Kigoshi

Claims 4, 49-51 and 53-56 all depend from claim 1, and so contain the same limitations as claim 1. If claim 1 is not anticipated by Miyajima or Kigoshi, neither are claims 4, 49-51 and 53-56.

Claim 1 is directed to a composition of matter comprising a spray dried solid dispersion, the dispersion portion of which "consists of" a drug having poor water solubility and HPMCAS, the drug being molecularly dispersed and amorphous in the dispersion. The transitional phrase "consists of" excludes from the list or phrase following it any ingredient not specified in the claim, *Ex parte Davis,* 80 USPQ 448, 450 (Bd App 1948), except for impurities ordinarily associated therewith. *Norian Corp. v. Stryker Corp.*, 70 USPQ 2d 1508, 1516 (Fed Cir 2004). Thus, the dispersion portion of claim 1 is directed to a two-component solid amorphous dispersion of low solubility drug and HPMCAS prepared by spray drying.

A claim is anticipated only if each and every element as set forth in the claim is found in the prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ 2d 1051, 1053 (Fed Cir 1987). Stated another way, the identical invention must be shown in the reference in as complete detail as set out in the claim. *Richardson v. Suzuki Motor Co.*, 9 USPQ 2d 1913, 1920 (Fed Cir 1989). Perhaps most importantly in this case, the anticipating reference must be sufficiently enabling to teach one of ordinary skill in the art how to make the claimed composition. *In re Donohue*, 226 USPQ 619, 621 (Fed Cir 1985).

As noted above, at best, Miyajima only teaches how to make three- and four-component compositions and none by spray-drying. Furthermore, Miyajima does not characterize the drug in the compositions as being amorphous or crystalline or a mix of amorphous and crystalline or in some other state. Because Miyajima does not disclose any two-component solid amorphous dispersion of low-solubility drug and HPMCAS by spray-drying, it does not identically disclose the claimed invention, and so Miyajima does not anticipate claims 1, 4, 49-51 and 53-56. In the same vein, Miyajima does not specifically teach how to make (*i*) any two-component dispersion of drug and HPMCAS alone or (*ii*) any dispersion by spray-drying. Miyajima is therefore non-enabling and so ineffective as an anticipating reference. *In re Donohue, supra*; *Akzo N.V. v. United States ITC*, 1 USPQ 2d 1241 (Fed Cir 1986).

As to Kigoshi, at best that reference discloses how to make a solid amorphous dispersion of a particular poorly soluble drug and a polymer by either fluid bed granulation or heat-melt-kneading with an extruder. As to Kigoshi's broader universe of potential processes for making such dispersions, at least 22 polymer choices are given

together with 15 different process choices, meaning that the universe of possible choices of polymer and method is at least 22 x 15, or 330. Based on this alone, it is respectfully submitted that Kigoshi does not anticipate. It is well-settled that anticipation may not be established by picking, choosing and combining various portions of a reference when those portions are not stated to be directly related to each other by the teachings of the reference. *Ex parte Beuther*, 71 USPQ 2d 1313, 1316 (Bd App 2003) (citing *In re Arkley*, 172 USPQ 524, 526 (CCPA 1972)). Accord, *Net MoneyIN, Inc. v. VeriSign, Inc.* 88 USPQ 2d 1751 (Fed Cir 2008).

Moreover, as is the case with Miyajima, Kigoshi does not specifically teach how to make either (*i*) any two-component dispersion of drug and HPMCAS alone or (*ii*) any dispersion by spray-drying. Thus, like Miyajima, Kigoshi is non-enabling and so ineffective as an anticipating reference.

Anticipation of claims 1, 4, 49 and 53-56 by JP 57

Claims 4, 49 and 53-56 all depend from claim 1. If claim 1 is not anticipated by JP 57, neither are claims 4, 49 and 53-56.

Since JP 57 gives no details whatsoever concerning how the reported spray-drying was conducted, the reference is non-enabling and so does not anticipate claim 1. *In re Donohue, supra*; *Akzo N.V. v. United States ITC, supra*.

Moreover, JP 57 neither discloses nor suggests any of the following claimed limitations: the drug is amorphous when undispersed (claim 4); the dispersion is spray dried particles that are solidified in less than 2 seconds (claim 49); the drug has a dose to aqueous solubility ratio greater than 100 (claim 53); and the drug is crystalline when undispersed (claim 54).

Obviousness of Claims 1, 23 and 50-51 in View of Miyajima or Kigoshi

Claims 23 and 50-51 all depend from claim 1. If claim 1 is not obvious in view of either Miyajima or Kigoshi, then neither are claims 23 and 50-51. *In re Fine*, 5 USPQ 2d 1596 (Fed Cir 1986).

As pointed out above, Miyajima does not in fact teach any spray-drying method of preparing any composition of drug and HPMCAS alone and does not characterize the compositions that are prepared as solid amorphous dispersions. Claim 1 is therefore not obvious in view of Miyajima.

As to Kigoshi, as also pointed out above, that reference does not disclose how to prepare (*i*) any two-component dispersion of drug and HPMCAS alone or (*ii*) any dispersion by spray-drying. Claim 1 is therefore not obvious in view of Kigoshi.

The Examiner is required to clearly articulate the reason or reasons why the claimed invention would have been obvious. *KSR Int'l. Co. v. Teleflex, Inc.*, 82 USPQ 2d 1385, 1396 (2007). Here, at pages 8-9 of the November 9, 2009 Office Action, as to claims 50-51 the Examiner merely states that claim 1 is anticipated by Miyajima and Kigoshi, that the residual solvent content in the Miyajima and Kigoshi formulations and the composition of the claims are the same except where "applicant shows that not to be the case" (as to Miyajima) and "there is factual evidence that it's not"(as to Kigoshi). It is respectfully submitted that the foregoing falls far short of the "clearly articulated reasons" standard of *KSR*. As to claim 23, the Examiner concedes that neither Miyajima or Kigoshi teach the less than 100 micron particle size claimed in claim 23,

but contends that Miyajima teaches a particle size of 100-400 mesh and Kigoshi teaches a particle size of 200 mesh, citing Example 1. The Examiner is quite mistaken. As to Miyajima, the 100-400 mesh the Examiner points to is the size of filler cores onto which the drug composition may be spray-coated. See Miyajima at page 5, lines 10-13. After such spray-coating, the Miyajima particle sizes are 355-400 microns. *Ibid*, page 6, Example 3, lines 33-36. As to Kigoshi, the 200 mesh of Example 1 is likewise a core of lactose onto which the composition was sprayed; there is no report on the particle sizes after the spray-coating.

Obviousness of Claims 1, 4, 36-37, 49-51 and 53-56 in View of Kigoshi, PubMed and Bymaster

Kigoshi is the primary reference relied upon for this rejection. Kigoshi fails to suggest the subject matter of claim 1 because, as pointed out above, the reference teaches 15 different processes with 22 different polymers and does not disclose how to prepare (*i*) any two-component dispersion of drug and HPMCAS alone or (*ii*) any dispersion by spray-drying. And neither PubMed nor Bymaster remedy these shortcomings of Kigoshi. Claims 4, 36-37, 49-51 and 53-56 all depend from claim 1 and so are likewise not rendered obvious by Kigoshi or the combination of Kigoshi with PubMed and Bymaster. *In re Fine, supra*.

There are other gaps in the Examiner's reasoning for this rejection. In paragraph 27 of the November 9, 2009 Office Action, the Examiner states, "Kigoshi has been described as teaching the limitations of claim 1 and dependent claims 4, 49-51 and 53-56." But a review of the Examiner's statements concerning the teachings of Kigoshi in

paragraph 12 bridging pages 5 and 6 of the Office Action show that her application of Kigoshi to claims 4, 49, 51 and 54 is based on limitations read into those claims that do not exist. Specifically, the Examiner states that the language of claim 4 that the "drug is amorphous when undispersed" means "claim 4 is also directed to the properties of the dosage form." But there is nothing in claim 4 concerning a dosage form or its properties. As to claims 49 and 54, the Examiner states that those claims "recite the properties of the composition." But claim 49 merely recites a limitation on the solidification speed (less than 2 seconds) of the spray dried particles. And claim 54 merely recites that the drug is crystalline when it is undispersed. As to claim 51, the Examiner states, "Claim 51 is a product by process claim." But claim 51 merely recites the parameters of the solution from which the particles are spray dried. When a rejection is based on mischaracterization of claims as is the case here, that rejection is submitted to be *per se* unsustainable as to those misconstrued claims.

Finally, the Examiner offers no explanation as to why one of ordinary skill in the pharmaceutical arts would be motivated to combine the teachings of PubMed and Bymaster with those of Kigoshi. PubMed merely reports that the drug risperidone is an effective antipsychotic for elderly patients. Not a word is found in PubMed as to the drug's solubility or how to incorporate the drug into any composition or dosage form. Bymaster is apparently relied upon to show that both risperidone and ziprasidone are known antipsychotics and so pharmaceutical equivalents. But Bymaster's invention is directed to a composition comprising one or two or more antipsychotics with one or two or more serotinin reuptake inhibitors. See Bymaster at column 3, line 62 to column 4, line 2. This being the case, where is the motivation for one of ordinary skill to choose

antipsychotic and form an amorphous dispersion of it? Note also that although Bymaster teaches eight different formulations for administering the inventive composition (at columns 11-13) he does not contemplate amorphous dispersions.

Conclusion

The rejections of claims 1, 4, 23, 36-37, 49-51 and 53-56 under 35 USC §102 and §103 are without merit and should be reversed.

Respectfully submitted,

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CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail on the date indicated below in an envelope addressed to: Mail Stop APPEAL BRIEF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

11/19/09
Date

Dennis E. Stenzel

CLAIMS APPENDIX

1. A composition of matter comprising a spray dried solid dispersion, which dispersion consists of a sparingly water-soluble drug and hydroxypropyl methylcellulose acetate succinate (HPMCAS), said drug being molecularly dispersed and amorphous in said dispersion and having a drug:polymer weight ratio between 1:0.4 and 1:20.

4. A composition as defined in claim 1, wherein said drug is amorphous when undispersed.

23. A composition as defined in claim 1, wherein said dispersion is in the form of particles less than 100 μm in diameter.

36. A composition as defined in claim 1 wherein said drug is an antipsychotic.

37. A composition as defined in claim 1 wherein said drug is ziprasidone.

49. A composition as defined in claim 1 wherein said dispersion comprises spray dried particles that are solidified in less than 2 seconds.

50. A composition as defined in claim 1 wherein said particles have a residual solvent content less than 2 wt%.

51. A composition as defined in claim 1 wherein said particles are spray-dried from a solution in which the concentration of drug in the solvent is less than 20 g/100 g and in which the total solids content is less than 25 weight%.

53. A composition as defined in claim 1 wherein said drug has a dose to aqueous solubility ratio greater than 100.

54. A composition as defined in claim 1 wherein said drug is crystalline when undispersed.

55. A composition as defined in claim 1 having a drug:polymer weight ratio between 1:0.5 and 1:20.

56. A composition as defined in claim 1 having a drug:polymer weight ratio between 1:1 and 1:20.

EVIDENCE APPENDIX

Not applicable.

RELATED PROCEEDINGS APPENDIX

Not applicable.